Durable remissions in TCF3-HLF positive acute lymphoblastic leukemia with blinatumomab and stem cell transplantation

Mouttet, Brice ; Vinti, Luciana ; Ancliff, Philip ; Bodmer, Nicole ; Brethon, Benoît ; Cario, Gunnar ; Chen-Santel, Christiane ; Elitzur, Sarah ; Hazar, Volkan ; Kunz, Joachim ; Möricke, Anja ; Stein, Jerry ; Vora, Ajay ; Yaman, Yöntem ; Schrappe, Martin ; Anak, Sema ; Baruchel, André ; Locatelli, Franco ; von Stackelberg, Arend ; Stanulla, Martin ; Bourquin, Jean-Pierre

DOI: https://doi.org/10.3324/haematol.2018.210104

haematologica
Journal of The Ferrata Storti Foundation

Durable remissions in TCF3-HLF positive acute lymphoblastic leukemia with blinatumomab and stem cell transplantation

by Brice Mouttet, Luciana Vinti, Philip Ancliff, Nicole Bodmer, Benoît Brethon, Gunnar Cario, Christiane Chen-Santel, Sarah Elitzur, Volkan Hazar, Joachim Kunz, Anja Möricke, Jerry Stein, Ajay Vora, Yöntem Yaman, Martin Schrappe, Sema Sanak, André Baruchel, Franco Locatelli, Arend von Stackelberg, Martin Stanulla, and Jean-Pierre Bourquin

Haematologica 2019 [Epub ahead of print]

Citation: Brice Mouttet, Luciana Vinti, Philip Ancliff, Nicole Bodmer, Benoît Brethon, Gunnar Cario, Christiane Chen-Santel, Sarah Elitzur, Volkan Hazar, Joachim Kunz, Anja Möricke, Jerry Stein, Ajay Vora, Yöntem Yaman, Martin Schrappe, Sema Sanak, André Baruchel, Franco Locatelli, Arend von Stackelberg, Martin Stanulla, and Jean-Pierre Bourquin. Durable remissions in TCF3-HLF positive acute lymphoblastic leukemia with blinatumomab and stem cell transplantation.
Haematologica. 2019; 104:xxx
doi:10.3324/haematol.2018.210104

Durable remissions in *TCF3-HLF* positive acute lymphoblastic leukemia with blinatumomab and stem cell transplantation

Brice Mouttet[1], Luciana Vinti[2], Philip Ancliff[3], Nicole Bodmer[1], Benoît Brethon[4], Gunnar Cario[5], Christiane Chen-Santel[6], Sarah Elitzur[7], Volkan Hazar[8], Joachim Kunz[9], Anja Möricke[5], Jerry Stein[10], Ajay Vora[3], Yöntem Yaman[8], Martin Schrappe[5,11], Sema Anak[8], André Baruchel[4], Franco Locatelli[2], Arend von Stackelberg[6], Martin Stanulla[12], and Jean-Pierre Bourquin[1]

[1] Pediatric Oncology, University Children's Hospital Zurich, 8032 Zurich, Switzerland
[2] Department of Pediatric Haemato-Oncology, IRCCS Ospedale Bambino Gesù, Roma, Sapienza University of Rome, Italy
[3] Haematology and Oncology Department, Great Ormond Street Hospital, London, United Kingdom
[4] Department of Pediatric Hematology, Hôpital Robert Debré, Assistance Publique – Hôpitaux de Paris, Paris, France
[5] Department of Pediatrics I, ALL-BFM Study Group, Christian-Albrechts University Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany
[6] Department of Pediatric Oncology/Hematology, Charité Universitätsmedizin, Berlin, Germany
[7] Pediatric Hematology-Oncology, Schneider Children's Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel
[8] Department of Pediatric Hematology, Medipol University Hospital, İstanbul, Turkey
[9] Pediatric Oncology, Hematology and Immunology, University of Heidelberg, Heidelberg, Germany
[10] Bone Marrow Transplant Unit, Schneider Children's Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel
[11] Pediatrics, Christian Albrechts University Kiel, University Medical Center, Kiel, Germany
[12] Pediatric Hematology and Oncology, Hannover Medical School, Hannover 30625, Germany

Corresponding Author

Jean-Pierre Bourquin, MD-PhD
Pediatric Oncology, University Children's Hospital Zurich, Zurich, Switzerland
8032 Zurich, Switzerland
Phone: +41 44 634 88 49
Fax: +41 44 266 3498
Email: Jean-Pierre.Bourquin@kispi.uzh.ch

TCF3-HLF positive leukemia represents a rare subtype of childhood acute lymphoblastic leukemia (ALL), characterized by a high rate of treatment failure despite treatment intensification and allogeneic stem cell transplantation (SCT). Given the high and homogenous expression of CD19 on blast cells of this leukemia subtype, these patients may benefit from CD19-directed immunotherapy. Here, we report the experience on nine *TCF3-HLF* positive ALL patients, most of which were treated early in first consolidation with blinatumomab as a bridge to SCT between 2015 and 2018. Treatment with blinatumomab was generally well tolerated; reversible neurotoxicity was observed in two patients. All nine patients achieved molecular remission after blinatumomab treatment, seven underwent SCT, for one patient SCT is planned. Median follow-up time after start of blinatumomab treatment was 342 days, and four patients remain in molecular remission after a follow-up of 1317, 1292, 1245 and 342 days, respectively. Three patients died because of infectious complications not directly related to blinatumomab, because they occurred after either SCT or emergence of a CD19-negative leukemia clone. In light of these encouraging observations, CD19-directed immunotherapy should be considered early after induction chemotherapy in *TCF3-HLF* positive ALL children and patients' outcome monitored systematically by study groups.

The chromosomal translocation t(17;19), resulting in the oncogenic fusion transcription factor TCF3-HLF[1], defines a rare cytogenetic subtype of B-cell precursor (BCP) ALL occurring in children and young adults that is associated with a dismal outcome[2]. Major leukemia study groups consider *TCF3-HLF* positive ALL patients eligible for addition of experimental therapies in first line. Functional screening of patient-derived xenografts revealed a dependence on BCL2 with promising response to a combination of venetoclax with vincristine and dexamethasone[3], which motivated the inclusion of a stratum allowing for combination of venetoclax with standard ALL therapy in the setting of a pediatric phase I/II study (NCT03236857)[4]. Moreover, given the strong homogeneous expression of CD19 in *TCF3-HLF* positive ALL and the impressive responses to CD19-directed immunotherapeutic approaches, these patients may benefit from CD19-directed immunotherapy[5].

Blinatumomab is a bispecific T-cell engager (BiTE®) antibody simultaneously binding CD3-positive cytotoxic T cells and CD19-positive B cells, resulting into a T-cell mediated serial lysis of B cells. Based on promising clinical activity with effective responses in heavily pretreated patients (NCT01466179)[6], blinatumomab gained accelerated

approval by the US FDA, EMA and Swissmedic agencies, for treatment of both children and adults with relapsed/refractory Philadelphia chromosome-negative BCP-ALL. Treatment with blinatumomab in adults with minimal residual disease-positive (MRD^+) ALL, mostly used as a bridge to stem cell transplantation (SCT), resulted into complete molecular response with MRD negativity in 80% of patients[7,8]. Similarly, high rate of molecular remission were confirmed in a larger clinical study enrolling adults patients in second or later morphological complete remission (CR)[9]. Extensive safety and efficacy data are available from pediatric patients included into a phase I/II study and an expanded access study (RIALTO) at a recommended Phase II dose of 15 $\mu g/m^2$/day continuous infusion (NCT02187354)[10]. In this first study, treatment of pediatric BCP-ALL patients with relapsed/refractory disease was initiated with high disease burden, given the endpoint requirements of the trial and only 16/62 patients for which MRD data was available achieved molecular CR, with a 24-month Kaplan–Meier estimate for overall survival of 25%[11]. The toxicity profile of blinatumomab is well established, including cytokine-release syndrome (CRS) and reversible neurologic events, such as ataxia, seizures and encephalopathy. The mechanisms leading to neurotoxicity remain unclear and may relate to variable expression of CD19 within the brain. Given the good tolerability and promising efficacy data, the potential benefit of blinatumomab improving outcome is being investigated in patients experiencing high-risk ALL first relapse (NCT02393859) and will be evaluated in first-line treatment in patients with intermediate and high-risk BCP-ALL by the AIEOP-BFM study group (NCT02393859).

Here, we report the European experience with blinatumomab using retrospectively collected data from nine patients with *TCF3-HLF* positive ALL that have been treated with blinatumomab between 2015 and 2018 by members of the international BFM study group after approval by the competent ethics committee; two of these 9 patients were enrolled in the expanded access protocol RIALTO. An overview of the patient data and clinical courses is provided in tables 1, 2 and figure 1.

Blinatumomab was initiated for disease refractory to induction chemotherapy (patient 1), for persistent MRD after consolidation chemotherapy (patients 3, 4, 5, 7, 8, 9), and after first relapse (patient 2, 6). Blinatumomab was administered at 15 $\mu g/m^2$/day for two to four cycles. All 9 patients responded, obtaining molecular CR after either the first cycle

(eight out of nine) or the second cycle (patient 7). Seven out of nine patients underwent allogeneic SCT after blinatumomab treatment. Details on the type of donor employed are shown in table 2. Four patients developed mild to moderate acute graft-versus-host disease (GvHD). No suitable donor could be found in time for patient 5, and this patient relapsed with CD19-negative leukemia blasts.

Four patients achieved a long-term remission and are still MRD negative after a follow-up of 1317, 1292, 1245 and 342 days, respectively (Figure 1). Given the expected risk for subsequent relapse, additional therapy was provided after SCT with one (patient 4) or two cycles (patients 2, 3) of blinatumomab. Three patients died from infectious complications: patient 4 due to a transplant-related adenoviral infection whilst in second molecular remission after her second SCT, patient 5 from a fungal infection whilst in CD19-negative relapse, and patient 6 from transplant-related aspergillus infection while in molecular relapse. Significant neurotoxicity occurred in two patients (Patients 1, 4). For patient 1, blinatumomab had to be interrupted due to confusion and decreased level of consciousness lasting 24 hours; it was resumed with a reduced dose of 5 µg/m^2/day and finally stopped because of seizures. This patient is currently still in molecular remission after SCT. Similar complications have been previously reported in pediatric patients[12,13]. Disseminated intravascular coagulation (DIC) was reported during treatment in two patients with overt leukemia, but was not considered to be treatment-related, because *TCF3-HLF* positive leukemia often present with coagulopathies. Patient 9 developed grade 2 CRS lasting for 48 hours. No other significant toxicity was reported.

This is the first report of clinical activity of CD19-directed immunotherapy in *TCF3-HLF* positive ALL, a rare BCP-ALL subtype reported to be almost always fatal even with most intensive conventional treatment regimens[2]. Although the number of patients treated is small and follow-up time limited, these results provide a strong rational for rapid intervention with immunotherapy for this ALL subtype. The response to blinatumomab has been reported to be less effective in patients with higher disease burden suggesting that this approach may be more effective in the MRD setting[6]. Current ongoing randomized pediatric studies will hopefully provide more evidence to answer this question. Until then, we recommend using a different treatment modality to reduce the leukemia burden before initiating blinatumomab. A conventional cytoreduction will also be required if immunotherapy with autologous CAR-T cell would be considered, allowing lymphapheresis and CAR-T cell manufacturing. Based on the current evidence, blinatumomab appears to be a promising therapeutical element to improve the quality of

remission in *TCF3-HLF* positive BCP-ALL patients as a bridge to SCT. In contrast, CAR-T might provide an attractive stand-alone treatment for definitive therapy without SCT. In general, this approach will have to be validated in clinical studies. Given the strong preclinical evidence for sensitivity to the BCL2 inhibitor venetoclax in most cases, including relapsing patients, combination of venetoclax with standard ALL chemotherapy may provide an additional treatment element improving outcome of these patients. Patients could be evaluated by functional screening using drug response profiling[3,14] and BH-3 profiling[15] at diagnosis. Three patients in this cohort have received additional courses of blinatumomab post-transplant for further consolidation of the leukemia remission, since even with MRD negative remissions prior to and after allogeneic HSCT, relevant rates of subsequent relapses are observed in *TCF3-HLF* positive ALL[2]. Persisting clones in compartments other than bone marrow may not be covered by MRD quantification but still be responsive to blinatumomab therapy. The responses detected in this *TCF3-HLF* positive ALL cohort are encouraging and suggest that the application of immunotherapy prior to extensive clonal selection secondary to intensive chemotherapy may be beneficial. We need to wait further maturation of the data to assess the true value of this approach. The benefit of adding blinatumomab to front-line ALL chemotherapy will be addressed in an international prospective clinical trial (NCT03643276). Taken together, our results indicate that immunotherapy may improve the outcome of *TCF3-HLF* positive ALL.

Acknowledgments

The authors thank Yun Huang (University Children's Hospital Zurich) for careful review of the manuscript and Renate Siegenthaler (University Children's Hospital Zurich) to provide data.

Authorship

Contribution: B.M. and JP.B. designed and performed the research, analyzed the data, and wrote the paper; L.V., P.A., N.B., B.B., C.CS., S.E., V.H., J.K., J.S., A.V., Y.Y., S.A., A.B., F.L., A.v.S., M.S. JP.B. managed treatment, provided data and reviewed the manuscript; G.C. A.M. and M.Sch. provided data and reviewed the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest disclosure: A.v.S. has received honoraria for invited presentations and has participated at advisory boards organized by Amgen, and has participated at advisory boards of the companies Novartis, Pfizer, Roche, Jazz-Pharmaceuticals and Morphosys. F.L. has received honoraria for invited presentations and has participated at advisory boards organized by Amgen. The other authors declare no competing financial interests.

Correspondence: Jean-Pierre Bourquin, Division of Oncology, University Children's Hospital Zurich, Children's Research Center, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland; e-mail: jean-pierre.bourquin@kispi.uzh.ch.

References

1. Inaba T, Roberts WM, Shapiro LH, et al. Fusion of the leucine zipper gene HLF to the E2A gene in human acute B-lineage leukemia. Science. 1992;257(5069):531–534.

2. Minson KA, Prasad P, Vear S, et al. t(17;19) in Children with Acute Lymphocytic Leukemia: A Report of 3 Cases and a Review of the Literature. Case Rep Hematol. 2013;2013(4):563291–563294.

3. Fischer U, Forster M, Rinaldi A, et al. Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. Nat Genet. 2015;47(9):1020–1029.

4. Place AE, Goldsmith K, Bourquin J-P, et al. Accelerating drug development in pediatric cancer: a novel Phase I study design of venetoclax in relapsed/refractory malignancies. Future Oncol. 2018;14(21):2115-2129.

5. Velasquez MP, Bonifant CL, Gottschalk S. Redirecting T cells to hematological malignancies with bispecific antibodies. Blood. 2018;131(1):30–38.

6. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol. 2015;16(1):57–66.

7. Topp MS, Kufer P, Gökbuget N, et al. Targeted Therapy With the T-Cell–Engaging Antibody Blinatumomab of Chemotherapy-Refractory Minimal Residual Disease in B-Lineage Acute Lymphoblastic Leukemia Patients Results in High Response Rate and Prolonged Leukemia-Free Survival. J Clin Oncol. 2011;29(18):2493–2498.

8. Topp MS, Gökbuget N, Zugmaier G, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood. 2012;120(26):5185–5187.

9. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018;131(14):1522–1531.

10. Stackelberg von A, Locatelli F, Zugmaier G, et al. Phase 1/2 Study in Pediatric Patients with Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) Receiving Blinatumomab Treatment. Blood. 2014;124(21):2292.

11. Gore L, Locatelli F, Zugmaier G, et al. Survival after blinatumomab treatment in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. Blood Cancer J. 2018;8(9):80.

12. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood. 2013;121(26):5154–5157.

13. Stackelberg von A, Locatelli F, Zugmaier G, et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. J Clin Oncol 2016;34(36):4381–4389.

14. Frismantas V, Dobay MP, Rinaldi A, et al. Ex vivo drug response profiling detects recurrent sensitivity patterns in drug-resistant acute lymphoblastic leukemia. Blood. 2017;129(11):e26–e37.

15. Deng J, Carlson N, Takeyama K, Dal Cin P, Shipp M, Letai A. BH3 Profiling Identifies Three Distinct Classes of Apoptotic Blocks to Predict Response to ABT-737 and Conventional Chemotherapeutic Agents. Cancer Cell. 2007;12(2):171–185.

Table 1: Clinical data of 9 patients with TCF3-HLF positive ALL treated with blinatumomab.

No.	Induction Treatment								Blinatumomab Treatment			
	Age (y)	Sex	WBC (nL)	Calcium (mmol/L)	EMD	Treatment Protocol	Prednisone Response	Disease Burden post induction	Disease Status prior to Blina	Disease Involvment	SAEs	Molecular Remission[5]
1	13	F	13.8	2.42	None	AALL 1131	N/A	FACS 27.5%	RD	BM	Depressed LOC	Yes
2	14	F	6.15	3.65	None	AIEOP-BFM	PPR	$< 10^{-3}_{4} > 10^{-}$	Relapse	BM	Bilateral hip osteonecrosis	Yes
3	8	M	14.49	2.57	CNS2b	AIEOP-BFM	PGR	10^{-2}	MRD	BM	None	Yes
4	7	F	5.26	3.2	CNS3	AIEOP-BFM	PGR	6×10^{-4}	MRD	BM	Convulsion CNS pleocytosis[2]	Yes
5	10	M	4.6	2.46	None	FRALLE	PGR	5×10^{-4}	MRD	BM	None	Yes
6	3	F	N/A	N/A	CNS2	AIEOP-BFM	PGR	negative	Relapse[4]	BM	None	Yes
7	8	F	11.3	N/A	None	AIEOP-BFM	PGR	7.5×10^{-3}	MRD	BM	None	Yes
8	5	F	25.7	2.63	None	UKALL	N/A	$3x\ 10^{-5}$	MRD	BM	None	Yes
9	7	M	8.2	5.03	None	AIEOP-BFM	PGR	3.2×10^{-3}	MRD	BM	CRS	Yes[1]

EMD, extramedullary disease; RD, refractory disease; BM, bone marrow; SAE, serious adverse events; LOC, loss of consciousness; CRS, Cytokine Release Syndrome

1: CNS pleocytosis without disease involvement
2: Initial diagnosis was c-ALL, isolated relapse under maintenance TCF3-HLF positive
3: Molecular Remission defined as per supplemental table 1
4: One marker positive non quantifiable, one marker negative after one cycle blinatumomab

Table 2: Definitive treatment of 9 patients with blinatumomab and outcome

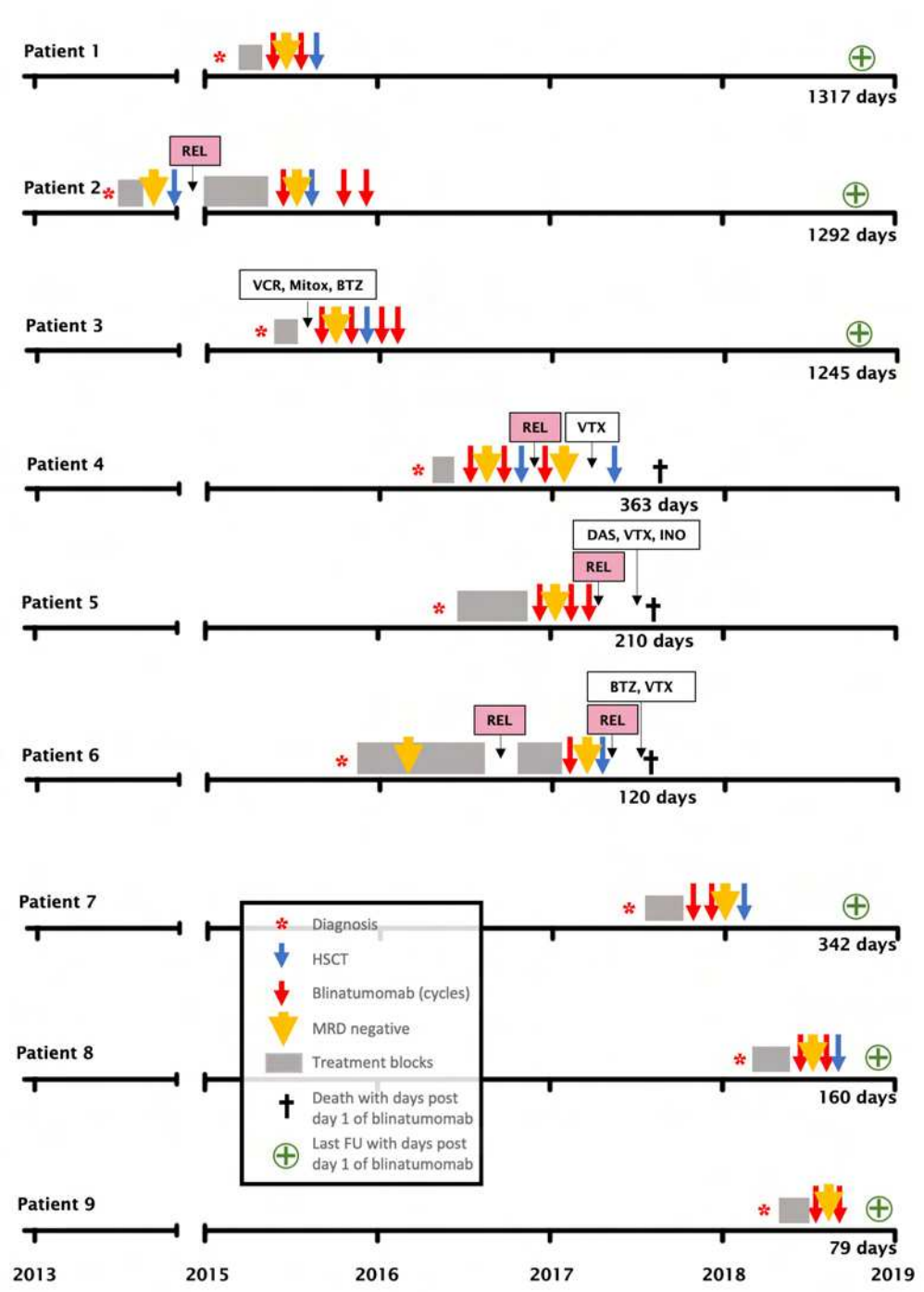
No.	HSCT				Current status	FU time (d)[6]
	Donor type for HSCT	Conditioning	GvHD Prophylaxis	GvHD		
1	Matched Unrelated	Bu, Thiotepa, Cy	CsA	Mild GvHD	ACR	1317
2	Matched Unrelated[1]	By, Cy, VP16, Thymoglobulin	CsA	Mild GvHD	ACR	1292
3	Matched Unrelated	TBI, VP16, ATG	CsA, MTX	Moderate GvHD	ACR	1245
4	Haploidentical[3]	Melphalan, Thiotepa, Fludarabine	Alemtuzumab, MM	No	Died from infection under remission	363
5	No HSCT	–	–	–	Died from infection under CD19-neg. relapse	210
6	Matched Related	TBI, VP16	CsA, MTX	Moderate GvHD	Relapse; Died from infection after HSCT	120
7	Haploidentical	TBI, Thiotepa, Fludarabine	None	No	ACR	342
8	Matched Unrelated	TBI, Cy	Alemtuzumab, CsA, MTX	No	ACR	160
9	No HSCT	–	–	–	ACR	79

MM, mycophenolate mofetil; ACR, alive and in complete remission

1: Patient underwent prior transplantation after induction but relapsed shortly after
2: Patient underwent prior transplantation after 2 cycles blinatumomab, but relapsed shortly after
3: Follow-up since first day of blinatumomab treatment

Figure 1: Time course of 9 patients with *TCF3-HLF* positive ALL treated with blinatumomab.

REL, relapse; VCR, vincristine; Mitox, mitoxantrone; BTZ, bortezomib; VTX, venetoclax; DAS, dasatinib; INO, inotuzumab


Patient 1
1317 days
REL
Patient 2
1292 days
VCR, Mitox, BTZ
Patient 3
1245 days
REL
VTX
Patient 4
363 days
DAS, VTX, INO
REL
Patient 5
210 days
BTZ, VTX
REL
REL
Patient 6
120 days
Patient 7
342 days
Patient 8
160 days
Patient 9
79 days
Diagnosis
HSCT
Blinatumomab (cycles)
MRD negative
Treatment blocks
Death with days post day 1 of blinatumomab
Last FU with days post day 1 of blinatumomab
2013
2015
2016
2017
2018
2019

Supplemental Table 1: Quantitative and Sensitivity Ranges of MRD markers, GvHD classification and additional clinical information.

No.	Quantitative Range			Sensitivity Range			GvHD classification	RIALTO	Molecular Diagnostic	Last MRD date (days post blina)	Blinatumomab Dosage (/m^2*d)				CD19 status at relapse	Cytogenetics at relapse
	Marker 1	Marker 2	Marker 3	Marker 1	Marker 2	Marker 3					Cycle 1	Cycle 2	Cycle 3	Cycle 4		
Patient 1	$5x\ 10^{-4}$	$5x\ 10^{-4}$	$5x\ 10^{-4}$	$1x\ 10^{-4}$	$1x\ 10^{-4}$	$1x\ 10^{-4}$	chronic	Yes	FISH	91	d1-d7: 5 µg, then 15 µg	5 µg	–	–	–	–
Patient 2	$1x\ 10^{-4}$	$1x\ 10^{-4}$	–	$1x\ 10^{-4}$	$1x\ 10^{-4}$	–	acute	Yes	FISH	1292	d1-d7: 5 µg, then 15 µg	15 µg	15 µg	–	–	–
Patient 3	$1x\ 10^{-3}$	$5x\ 10^{-4}$	–	$5x\ 10^{-4}$	$1x\ 10^{-5}$	–	chronic	–	FISH (Cytocell)	489	15 µg	15 µg	7.5 µg	15 µg	–	–
Patient 4	$1x\ 10^{-4}$	$1x\ 10^{-4}$	–	$1x\ 10^{-4}$	$1x\ 10^{-5}$	–	–	–	FISH (Cytocell)	–	15 µg	15 µg	15 µg	–	positive	unchanged
Patient 5	$1x\ 10^{-4}$	–	–	$1x\ 10^{-5}$	–	–	–	–	RT-PCR	–	15 µg	15 µg	15 µg	–	negative	not performed
Patient 6	$1x\ 10^{-4}$	$1x\ 10^{-4}$	–	$1x\ 10^{-5}$	$1x\ 10^{-5}$	–	acute	–	RT-PCR and FISH	–	15 µg	–	–	–	positive	unchanged
Patient 7	$1x\ 10^{-4}$	$1x\ 10^{-4}$	–	$1x\ 10^{-5}$	$1x\ 10^{-5}$	–	–	–	RT-PCR[1]	300	15 µg	15 µg	–	–	–	–
Patient 8	$1x\ 10^{-4}$	$1x\ 10^{-4}$	–	$1x\ 10^{-4}$	$1x\ 10^{-4}$	–	–	–	FISH (Cytocell)	50	15 µg	15 µg	–	–	–	–
Patient 9	$1x\ 10^{-4}$	$5x\ 10^{-4}$	–	$1x\ 10^{-5}$	$1x\ 10^{-4}$	–	–	–	RT-PCR[1]	71	15 µg	15 µg	–	–	–	–

RIALTO, Blinatumomab in Pediatric & Adolescent Subjects With Relapsed/Refractory B-precursor ALL (NCT02187354)

1: RT-PCR reference: van der Velden VH, et al. Leukemia. 2007 Apr;21(4):706-13